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CORRESPONDENCE

"Hypothesis: Patient with possible disturbance in programmed cell death": further insights in pathogenicity and clinical features of Fraser syndrome

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TO THE EDITOR:

In 1995, Hennekam and Cohen described a patient with an unknown syndrome of which they suspected a disturbed programmed cell death to be the cause [1]. This male had complete cutaneous syndactyly of the hands and feet, underdeveloped lacrimal ducts, narrow external ear canals, pharyngeal mucous membrane fold, unilateral cryptorchidism, bilateral cord-like vasa deferentia without a lumen and small epididymis.

Twenty-seven years later, we had the opportunity to re-study the patient and were able to detect the molecular background in this patient. The clinical phenotype was compatible with an unusual form of Fraser syndrome, so we screened through next generation sequencing the four known Fraser syndrome genes (*FRAS1, FREM1, FREM2, GRIP1)* and identified two compound heterozygous *FRAS1* variants (NM_025074.6:c.8353del p.(Val2785Trpfs*33) (pathogenic) and c.1724G > A p.(Cys575Tyr) (likely pathogenic)). The original authors had already mentioned that the clinical features were reminiscent of Fraser syndrome, but at that time the patient did not fulfill the clinical criteria. However, the phenotype was now found to fulfill the present diagnostic criteria [2]. The molecular confirmation aided the patient to understand his phenotype and allowed his family-members to make informed decisions regarding reproduction.

The hypothesis suggested by Hennekam and Cohen that a disturbed programmed cell death could be the underlying pathology, was well estimated. The Fraser complex including FRAS1 is composed of extracellular matrix proteins, which are critical for the regulation of epidermal basement membrane adhesion and epidermal blistering [3]. It has been suggested that a loss of function of the Fraser complex thereby leads to disturbed programmed cell death and initiation of the kidney [4, 5], which likely explains most of the characteristics of our patient. To our knowledge, atresia of the vas deferens and a small epididymis have not previously been described in males with Fraser syndrome. Analyses of *CFTR* did not show any abnormalities and made Cystic fibrosis as an alternative cause unlikely. It is plausible that atresia of the vas deferens and the small epididymis can be part of the Fraser phenotype, since programmed cell death and blistering are involved in the fusion of the cloaca and mesonephric duct, from which the vas deferens and epididymis are formed during embryogenesis [5]. We suggest that examination of reproductive structures should be part of the clinical work up when establishing a diagnosis of Fraser syndrome, and it may be useful to evaluate individuals with (presumed) isolated vas deference atresia for variants in one of the genes known to cause Fraser syndrome.

Lynne Rumping [1]✉, Raoul C. M. Hennekam[1], Mariëlle Alders[1] and Mieke M. van Haelst[1]
[1]*Department of Human Genetics, Amsterdam University Medical Center, Amsterdam 1105 AZ, The Netherlands.*
✉*email: lynne.rumping@uza.be*

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

All authors were involved in the clinical care of the patients. LR drafted the paper and all authors critically revised and approved the final version of the paper.

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COMPETING INTERESTS

The authors declare no competing interests.

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ETHICS APPROVAL

Ethics approval is not applicable for this paper, as this concerns a clinical case report of a patient from whom we have obtained informed consent.

CONSENT TO PARTICIPATE

Written informed consent for participation and publication was obtained.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Lynne Rumping.